

## An Effective Scientific Strategy for Assessing Harm Reduction Potential in Cigarettes

R. J. Reynolds Tobacco  
Company

## Agenda

### Overview of Scientific Strategy

Dr. J. Donald deBethizy

### Step 1: Smoke Chemistry

Dr. Michael Borgerding

### Step 2: Toxicology Assays

Dr. David Doolittle

Dr. Arnold Mosberg

## Agenda

### Step 3: Clinical Studies

Dr. John Robinson - Smoking Behavior

Dr. David Doolittle - Surrogate Markers

### Lessons Learned

Dr. J. Donald deBethizy

### Summary

## RJRT's Risk Reduction Goal

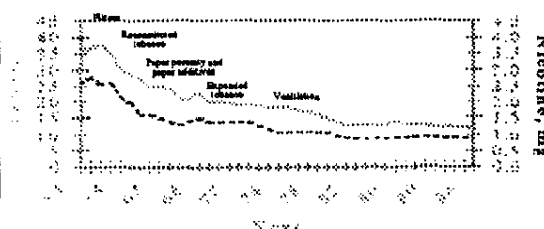
To develop and market commercially-  
viable, reduced-risk cigarettes for  
smokers who won't quit.

## Historical Perspective General Reduction Strategy

- ◆ Reduce "tar" and nicotine yields
  - ◆ Filters
  - ◆ Reconstituted Tobacco Sheet
  - ◆ Porous Paper
  - ◆ Filter Ventilation
  - ◆ Expanded Tobacco

## Progress and Limits of General Yield Reduction Approach

*US Sales-Weighted Average 'Tar' and Nicotine Yields*



### General Reduction Approaches Have Matured in the Marketplace

- ♦ The sales weighted average yields of nicotine and "tar" have stabilized
- ♦ The composition of "tar" has remained generally constant
- ♦ Smokers unwilling to move lower in "tar"
- ♦ Smoking behavior can limit effectiveness

### Further Reductions in Risk Require

- Further reduction in "tar" yield
- Change "tar" composition
- Selective component reduction

### Strategy to Assess Risk Reduction

### Key Facts

- Cigarettes carry significant, inherent health risks for serious diseases including CVD, COPD, and cancer
- Known cigarette technology cannot produce a commercially viable "safe" cigarette
- Reduced risk or harm must be based on comparisons to today's cigarettes

### Weight of the Evidence Approach

- There are no animal models that are direct measures of cigarette smoking related diseases
- Lack of clear mechanisms make it difficult to focus on specific compound reductions or single biological endpoints

### A Weight of Evidence Approach

- Assays are available and appropriate to compare differences in:
  - Chemistry
  - Toxicity
  - Smoking Behavior
- The patterns of changes in chemistry, exposure and biology must be considered as a whole.
- Experts must weigh the evidence and extrapolate to assess harm-reduction potential.

### Step 1 Reduced Smoke Chemistry

- Toxicity of cigarette smoke results from:
  - Chemical composition of the smoke
  - Degree and nature of the smoker's exposure
- Reduced risk cigarettes must reduce the amount of tobacco burned and/or simplify the chemical composition of the smoke.
- Reduced risk cigarettes must also reduce the exposure to harmful chemicals in smoke.

### Step 2 Reduced Smoke Toxicity

- Chemical reductions alone cannot predict reduced toxicity
- No single assay can directly measure disease risk
- Battery of preclinical and clinical studies must be used to indicate the biological significance of the chemical changes

### Step 3 Reduced Effects in Humans

- Tests in smokers assess effects under actual smoking conditions
- Markers are used to assess exposure and harm-reduction potential

### Expert Opinion and Accepted Practice form the Foundation of the Assessments

- Chemistry approach is based on published methods and the development of new techniques
- Toxicology assays are based on published government and industry-accepted methods
  - In Vitro (CAAT, ICH, EPA, FDA and Literature)
  - In Vivo (NCI, OECD, NTP, EPA, FDA and Literature)
- Behavioral measurements in smokers have been developed and published at RJRT
- Markers in clinical studies were selected and measured by clinicians

### Summary of Effective Strategy for Assessing Risk Reduction in Cigarettes

#### Reduction of Chemical Substances

- Smoke Chemistry Studies

#### Less Toxicity

- In Vitro Toxicity Studies
- Animal Toxicity Studies

#### Reduced Effects in Smokers

- Smoking Behavior/Exposure Assessment
- Clinical Studies using Markers